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Impacts Of Sugar On Pediatric Oncological Treatment

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ABSTRACT
Pediatriccancerisoneoftheleading causes ofchildhoodmortality, andtheimpactofdietaryfactors, such as excessive sugar consumption, ontheprogressionandtreatmentoftumors in childrenhasgarneredincreasinginterest. Thisstudy reviews theliteratureontheinfluenceof sugar on tumor metabolism, highlightingthe Warburg effect, wherecancercellspreferentially utilize anaerobicglycolysis for energyproductioneven in thepresenceofoxygen, promoting tumor proliferation. Furthermore, high sugar intakeisassociatedwithincreasedinsulinand IGF-1 levels, whichsupportthegrowthof tumor cells, as well as exacerbatingchronicinflammationandimmunosuppr ession, compromisingtheimmunesystem's response. Dietarystrategies, such as sugar restriction, haveshowntherapeuticpotentialbyreducingthe glucose availableto tumor cells, althoughtheyshouldbeimplementedcautiously in pediatricpatientsduetotheircriticalnutritionalneeds for development. Thisarticleemphasizestheimportanceoffurtherresear chthatintegratespediatriconcology, nutrition, andmetabolism, aiming for personalizedinterventionsthatmayenhanceclinicalou tcomesandthequalityoflife for childrenundergoingcancertreatment.
KEYWORDS: SUGAR, NEOPLASM, PEDIATRICS, TREATMENT.

I. INTRODUCTION

Pediatriccancerisoneoftheleading causes ofmortality in childrenandadolescents, surpassedonlybyaccidents in termsof global incidence. Althoughadvances in oncologicaltreatmentshavesignificantlyincreasedsur vival rates over thepast 50 years, reachingaround85% for mosttypesofchildhoodcancer, prognosisand response totreatment still varywidely, dependingonbiologicalandenvironmentalfactors (American Cancer Society, 2024). In thiscontext, thereisgrowinginterest in investigatinghowdietaryfactors, such as excessive sugar consumption, mayinfluencetheprogressionandtreatmentofneoplas ms in pediatricpatients.

The alteredmetabolismofcancercells, characterizedbythephenomenonknown as the Warburg effect, plays a central role in cancerbiology. In thisphenomenon, even in thepresenceofoxygen, tumor cellsprefertogenerateenergymainlythroughanaerobi cglycolysisratherthanmitochondrialoxidativephosp horylation, resulting in lactateproductionand promoting tumor growth (Isidoro; Cuezva, 2004). The high rate of glucose uptakebycancercellsisoneofthemarkersofthisconditi on, suggestingthatexcess sugar in the diet couldpotentiallyprovide more substrate for tumor growthandproliferation.

In addition, excessive sugar consumptionisassociatedwithelevatedlevelsofinsuli nandinsulin-like growthfactor (IGF-1), hormonesthatcanpromote tumor cellsurvivalandproliferation (Gallagher; LeRoith, 2020). Thesegrowthfactors are recognized for theirmitogenic, anti-apoptotic, and pro-inflammatoryactions, whichcreate a biologicalenvironmentconduciveto tumor progression, especially in individualswith a high intakeofrefinedsugars.

The impactof sugar ontheimmune system alsodeservesattention. High sugar consumptioncanexacerbateoxidative stress andchronicinflammation, theprocesscontributestoimmunosuppressionandcom promisestheimmunesystem'sabilitytoidentifyanddes troycancercells. Furthermore, the Fenton and Haber-Weiss reactions, whichgeneratereactiveoxygenspecies (ROS) in sugar-richenvironments, can cause significant DNA damage, increasegenomicinstability, andpromotecarcinogenesis (Murphy et al., 2014).

Giventhisevidence, thisstudyseeksto explore, through a literature review, theimpactofexcessive sugar consumptionontheprogressionandtreatmentofneoplasms in pediatricpatients. The objectiveistoassesswhetherreducing sugar consumptioncouldcontributetoimprovingtherapeuticoutcomesandprognosisbymitigating tumor promotionmechanisms, inflammation, andimmunosuppression.

II. METHODOLOGY

Thisworkadoptsthestudymethodologyproposedby Gil (2008), characterized as a bibliographic review. Accordingtotheauthor, thismethodologyinvolvestheanalysisofpreviouslyelaborated material, suchas booksandscientificarticles.

In thiscontext, theresearchcarries out a systematicliterature review withtheobjectiveofexploringtheimpactof sugar consumptiononpediatriconcologicaltreatment. The central hypothesisofthisstudyisthatreducing sugar consumption in pediatricpatientswithneoplasmscan improve treatmentoutcomesbypositivelyinfluencingfactorssuch as cancercellbehavior, chronicinflammation, insulinresistance, andimmunefunction, resulting in a more effectivetherapeutic response and a more favorableprognosis.

Toconductthis review, thework follows a methodologicalsequencethat includes thefollowing steps: definitionoftheresearchquestion, searchofscientificdatabases, selectionofrelevantstudies, data extractionandanalysis, and, finally, presentationanddiscussionoftheresults.Forthestudysearch, recognizedelectronicdatabasessuch as PubMed, Scopus, and SciELO werechosen. The searchwillbecarried out usingspecificterms, such as "Warburg effect," "insulin-like growthfactor (IGF-1)," "oxidative stress," andtheirvariations, combinedwithBooleanoperators. The searchwaslimitedtostudiespublished in thelast7years (2018-2024), in English, focusingontheimpactsof sugar onthetreatmentofchildrenwithcancer.

Afterscreeningthetitlesand abstracts, thestudiesdeemedmostrelevant for detailedanalysiswereselected. The criticalevaluationoftheselectedstudieswillbecarried out consideringbothmethodologicalqualityandrelevance totheresearchquestion. For data extraction, a standardizedformwillbeused, whichwill include informationonthestudy design, sample characteristics, possibleimpactsof sugar onmetabolismandcancercells, as wellas itsinfluenceonpediatriconcologicaltreatment. The mainresultsandconclusionsofthestudieswillalsoberecorded.

The synthesisoftheresultswillbeconductedthroughqualitativeanalysis, withtheobjectiveofidentifying trends anddiscrepanciesamongthereviewedstudies. The discussionwilladdresstheclinicalimplicationsofthefindings, as well as themethodologicallimitationsofthestudiesincluded in the review, in ordertoprovide a comprehensiveanalysisoftheevidence. The focusoftheanalysiswasdefined as thestudy'sobjective, methodologicalquality, andoutcome, andtheQualis (Brazilianscientificjournal ranking platform) rating ofthejournal in whichthearticleswerepublishedwasverified.

In additiontothis approach, thestudyadopts as a secondmethodologicaloptionthe 2020 PRISMA (PreferredReportingItems for Systematic Reviews and Meta-Analyses) guideline. PRISMA is a widelyrecognized set of standards for thetransparentconductandpresentationofsystematic reviews and meta-analyses. The adoptionof PRISMA allows for a clearvisualizationofthenumberofstudiesidentified, selected, andincluded in the review through a flowchart, contributingtothetransparencyandreproducibilityoftheprocess (Page et al., 2021). The searchandselectionstrategyusedwillbedetailed in the PRISMA flowchart, whichwillbepresentedin Figure 1.

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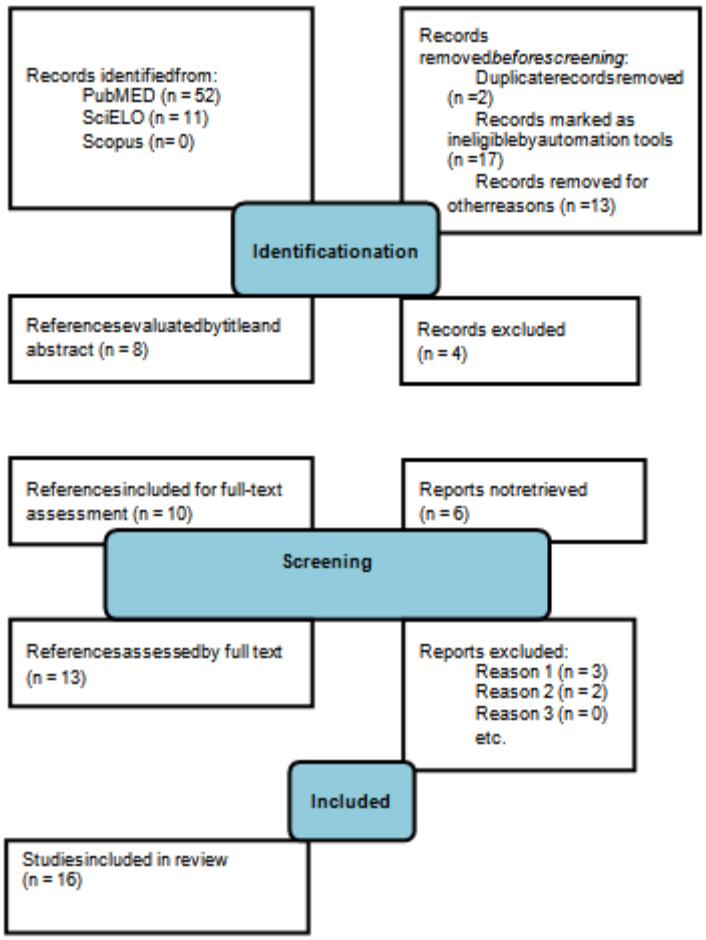
Figure 1. Flowchart ofarticleselectionbasedonestablishedcriteria.



III. RESULTS

TITLE	AUTHOR AND YEAR	OBJECTIVE	MAIN RESULTS/CONCLUSION
Total sugar andadded sugar intake, typesof sugar, andcancerrisk: resultsfromtheprospectiveNutriNet-Santé cohort	Debras C, Chazelas E, Srour B, et al. 2020	The objectivewastostudytheassociationsbetween total andadded sugar intakeandcancerrisk (overall, breast, andprostatecancer), consideringtypesandsourcesof sugar.	Total sugar intakewasassociatedwithanincreasedcancerrisk, especiallybreastcancer.
Significanceoflow-carbohydrate diets andfasting in patientswithcancer	AlicjaSzypowska 1, BożenaRegulska-Ilow 1	The study'sobjectivewastodiscussthe relationshipbetweenlow-carbohydrate diets andfastingduringcancertreatment, exploringhowthesedietary approaches canaffecttheeffectivenessofconventionaltreatments.	The resultsindicatedthatpatientswho maintainedlow-carbohydrate diets showedimproved overall health, a reduction in tumor mass, andslower tumor growth. The studyalsosuggestedthatfastingcould make cancercells more sensitivetochemotherapy,

			reducegrowthfactorconcentrations, andpromote normal cellrepair. Additionally, fastingwasobservedtoinduceautophagy, a processthatcansimultaneouslyeliminatecancercells.
CarbohydrateNutritionandtheRisk of Cancer	Maino Vieytes, Christian A et al. 2019	The objectiveofthe review wastosummarizeepidemiologicalstudiesinvestigatingtheassociationsbetweencarbohydrateintakeandcancerincidenceandsurvival, consideringbiologicalmechanismsthatmayexplaintheseassociations.	The conclusionofthe review indicatesthattheevidenceontherelationshipbetweencarbohydratesandcancerriskisstrongest for theassociationbetweenfiberandcolorectalcancer, withincreasedfiberintakeassociatedwithreducedrisk.
Metabolicbarrierstocancerimmunotherapy	DePeaux, Kristin, and Greg M Delgoffe. 2021	The objectiveofthestudywastoinvestigatehowthecharacteristicsofthe tumor microenvironment (MET) affecttheimmune response ofantitumor T cellsandhowmetabolicrestrictions in thisenvironmentcanbeovercome to improve cancerimmunotherapy.	The study'sresultsindicatethatinterventionsovercomingmetabolicrestrictions in the tumor microenvironment—such as low glucose levels—show potentialwhencombinedwiththerapiessuch as immune checkpoint blockade, adoptivecelltherapy, andoncolyticvirustherapy, improvingimmunotherapyefficacyand tumor control.
Simple sugar intakeandcancer incidence, cancermortality andall-cause mortality: A cohortstudyfromthe PREDIMED trial	Laguna, Juan C et al. 2021	To examine therelationshipbetweensimple sugar intakeandtheincidenceofcancer, cancermortality, andall-cause mortality in a cohortof high cardiovascular riskindividuals.	However, anincreaseof 5 g/day in liquid sugar intakewasassociatedwith a highercancerincidence, with a cancerriskratiorangingfrom 1.08 for total liquid sugar to 1.39 for fructosefromfruitjuice. Mortalityduetocancerandall causes alsoincreasedwithliquid sugar intake.
Sugar Free: Novel Immunotherapeutic Approaches TargetingSiglecsandSialicAcids toEnhance Natural Killer CellCytotoxicity Against Cancer	John Daly 1, MattiasCarlsten 2, Michael O'Dwyer 1. 2019	The review investigatesthe role ofinhibitoryreceptors Siglec-7 and Siglec-9 on Natural Killer (NK) cellsandtheirinteractionwithsialylated surfaces of tumor cells, focusingonhowtheseinteractions regulate NK cellcytotoxicityandimmuneevasionbycancercells.	Recentevidenceindicatesthatthesialylatedglycanlayeroncancercellsfacilitatesimmune system evasion. Thishypersialylation interferes with NK cellactivity, allowingtumorsto escape immunesurveillance. Siglec-7 and Siglec-9 inhibitoryreceptors, whichinteractwithsialylatedglycans, show therapeuticpromise.
Effectsof Glucose Metabolism, LipidMetabolism, andGlutamineMetabolismon Tumor	Zhu, Longfeiet al. 2022	Toinvestigatetheinfluenceofmetabolicpathways, particularly glucose andlipidmetabolism, in the tumor microenvironmentandhowthese alterationsaffectcancertherapies, with a focuson glucose metabolismreprogrammingand	The researchhighlightsthat sugar metabolism, particularlythroughglycolysis, plays a crucial role in the tumor microenvironment. Tumor cells consume largeamountsof glucose, generatinglactate, contributingtoanimmunosuppres

Microenvironment and Clinical Implications		its impact on immune response.	sive environment that affects NK cell function and limits the effectiveness of immunotherapy.

Studies such as Debras et al. (2020) indicate that sugar intake, especially added sugars, is associated with an increased risk of cancer, particularly breast cancer. Although the focus is on adults, these findings provide an important basis for investigating the impact of sugar consumption in pediatric oncology patients, considering that sensitivity to sugar may be amplified due to still-developing metabolic characteristics. This scenario also raises concerns about the impact of excessive simple sugar consumption in pediatric patients, as altered metabolism may aggravate the tumor microenvironment (Szypowska; Regulska-Ilow, 2019).

Furthermore, the use of low-carbohydrate diets and fasting strategies has been explored, presenting potential implications for pediatric oncology. Such approaches, according to Szypowska and Regulska-Ilow (2019), may improve the efficacy of conventional treatments, such as chemotherapy, by promoting autophagy and reducing the concentration of tumor-stimulating growth factors. However, in children, caution is essential when implementing restrictive diets, as nutritional requirements are critical during growth, reinforcing the need for a personalized approach.

Vieyte et al. (2019) corroborate these findings by highlighting that the consumption of refined carbohydrates and simple sugars is associated with an increased risk of various cancers. The quality of carbohydrates in the diet of children undergoing oncological treatment is, therefore, a factor to consider, prioritizing fiber-rich foods and limiting processed sugar intake. Laguna et al. (2021) also identified a correlation between the consumption of liquid sugars, such as those found in sweetened beverages, and an increase in cancer incidence and overall mortality, suggesting that moderation in the consumption of these products may be beneficial for pediatric patients.

Another important aspect is the impact of sugar metabolism on the tumor microenvironment and immune response. According to DePeaux and Delgoffe (2021), tumor cells consume large amounts of glucose, creating an immunosuppressive environment that inhibits the action of T cells and Natural Killer (NK) cells, which are essential in the antitumor response. This is particularly concerning in children, whose immune systems are still developing, making sugar intake control necessary to enhance the immune response during therapy. Additionally, Daly et al. (2019) explain that the metabolism of sialylated glycans in tumor cells allows them to evade immune surveillance by interacting with Siglec-7 and Siglec-9 receptors on NK cells, reinforcing the importance of dietary interventions that reduce available glucose for these interactions.

Zhu et al. (2022) point out that excessive glycolytic metabolism in tumor cells results in lactate production, contributing to an immunosuppressive microenvironment, which may further impair the efficacy of immunotherapies such as immune checkpoint blockade. This factor is especially relevant in pediatric treatments, where controlling dietary glucose can be a valuable tool to optimize the immune response and increase the efficacy of therapies.

Another point discussed is the Crabtree effect, which demonstrates that the presence of glucose inhibits cellular respiration and favors glycolysis. In Crabtree-positive cells, such as Saccharomyces cerevisiae, there is a shift from respiratory metabolism to respiro-fermentative metabolism in high glucose, affecting the cell cycle and ATP production. This metabolic shift favors lactate production and tumor microenvironment acidification, contributing to cancer progression (Alteriis et al., 2018). The predominance of glycolysis over oxidative phosphorylation in tumor cells highlights the importance of strategies that aim to inhibit this pathway as a means of controlling tumor growth (Vaupel; Schmidberger; Mayer, 2019).

Understanding these metabolic adaptations, as discussed by Pascale et al. (2020), can enrich therapeutic approaches in cancer treatment. The use of glycolytic enzyme inhibitors, such as 2-deoxyglucose (2-DG), is being explored to potentiate the effects of conventional therapies. However, any dietary intervention must be monitored, especially in pediatric patients, to ensure their nutritional needs are met.

Studiessuggestthat in thepresenceof high glucose concentrations, theactivityoftheelectrontransportchain (OXPHOS) isreduced, favoringfermentation over mitochondrialrespiration, which maximizes energyproductionrapidlyandpromotes tumor growth (Alberghina, 2023). Thisinformationreinforcestheimportanceoftherapeuticstrategiesaimedatmodulatingcellularmetabolism, understandingtheinteractionsbetweenglycolyticpathwaysand tumor growth, toimplementinterventionsthattreatthediseasewhilerespectingthemetabolicneedsofgrowingchildren (Pascale et al., 2020).

IV. CONCLUSION

Interactionbetween sugar consumptionandpediatriconcologicaltreatmentisanemergingfieldthatdemandsattentionduetothemetabolicparticularitiesofchildren. High intakeofsimplesugarscanimpact tumor progressionandimmune response. Pediatricpatients are particularlysensitivetodietaryinfluences, especiallyduringchemotherapyandimmunotherapy, wheremodulationof sugar metabolismcan improve clinicaloutcomes.

Furthermore, theinhibitionofglycolyticpathways, such as the use of 2-deoxyglucose (2-DG), offerspromising prospects but requires carefulmonitoringtoensurethatchildrenreceivethenecessarynutrients. Thus, thereis a need for more studiesintegratingpediatriconcology, nutrition, andmetabolism.

Additionalresearchisessentialtodeveloppersonalized strategiesthatmeetnutritionalneedsandoptimizeoncologicaltreatments, improvingqualityoflifeandincreasingsurvival rates in pediatric oncology.

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